



## Therapeutic Class Review<sup>SM</sup>

### Antineoplastics – nilotinib (Tasigna<sup>®</sup>)

October 2008

**New Product for Review:**  
nilotinib (Tasigna<sup>®</sup>) [Novartis]

**Dossier Provided by Manufacturer: Yes**

**Dossier Evaluation: 3**

- 1 - Dossier missing significant clinical trial(s).
- 2 - Mfg. provided all relevant trials; Missing pharmacoeconomic model.
- 3 - Mfg. provided all relevant trials and information.

#### Executive Summary

##### *Chronic Myelogenous Leukemia (CML)*

- CML is a myeloproliferative disorder.
  - The annual incidence rate is 1.6 cases per 100,000 adults.<sup>[1]</sup>
  - There are approximately 4,600 new cases diagnosed in the U.S. each year.<sup>[1]</sup>
- The Philadelphia chromosome, which results from a gene translocation, is implicated in the pathogenesis of CML.<sup>[1]</sup> The Philadelphia chromosome can be identified in 95% of adults with CML.
- CML may occur in the chronic phase, accelerated phase, or blast crisis.<sup>[1]</sup>
  - The majority of patients are diagnosed with chronic phase CML.
  - Untreated, chronic CML progresses to the more aggressive accelerated and blast phases after 4 to 5 years.
  - Median survival of patients in blast crisis is 6 months.

##### *Treatment of CML*

- Allogeneic stem cell transplantation is the only treatment proven to cure CML, but may not be an option for all patients.<sup>[1]</sup>
- Imatinib (Gleevec) is currently the treatment of choice for most newly diagnosed patients with CML.<sup>[1]</sup>
  - The goal of therapy is to reduce the number of cells that contain the Philadelphia chromosome.
  - The duration of therapy is indefinite as nearly all patients relapse once imatinib is discontinued.

- Dasatinib (Sprycel) and nilotinib (Tasigna) may be useful in treating patients with CML who are resistant to, or intolerant of, imatinib (Gleevec).
- Comparison of FDA-approved indications for tyrosine kinase inhibitors used in CML:

Medication	CML phase			Ph+ALL	MDS	Masto-cytosis	HES/CEL	GIST
	Chronic	Accelerated	Blast					
dasatinib (Sprycel)	X	X	X	X				
imatinib (Gleevec)	X	X	X	X	X	X	X	X
nilotinib (Tasigna)	X	X						

Ph+ALL: Philadelphia chromosome-positive acute lymphoblastic leukemia; MDS: myelodysplastic syndromes; HES/CEL: hypereosinophilic syndrome/chronic eosinophilic leukemia; GIST: gastrointestinal stromal tumor

- Current National Comprehensive Cancer Network (NCCN) guidelines place dasatinib (Sprycel) and nilotinib (Tasigna) as second-line agents in the treatment of CML. <sup>[2]</sup>

### Evidence

- There is no reliable evidence supporting the efficacy of nilotinib (Tasigna) in Ph+ CML.
  - There were no placebo or active comparators employed in the trials.
  - Not all patients that were treated were analyzed for the efficacy endpoint (selection bias).
- In addition, there is no reliable evidence:
  - Comparing the safety and efficacy of nilotinib (Tasigna) with dasatinib (Sprycel) in Ph+ CML.
  - Supporting the efficacy of nilotinib (Tasigna) in patients who have not responded to dasatinib (Sprycel) in the treatment of Ph+ CML.
- Safety information from the nilotinib (Tasigna) study is difficult to interpret due to lack of placebo or active comparators and the relative short duration of the studies.

### Decision

Nilotinib (Tasigna) is non-preferred/non-formulary because there is no useful evidence demonstrating its safety or efficacy in the treatment of CML.

## Products

Drug Products	FDA approval <sup>a</sup>	Patent Expiration(s) <sup>b</sup>	FDA approved indications	Usual Dose/Route	Potential Off-label Uses <sup>c</sup>
dasatinib (Sprycel <sup>®</sup> ) <sup>[4]</sup>	6/2006	4/2020	<ul style="list-style-type: none"> <li>Chronic, accelerated, or myeloid or lymphoid blast phase CML in patients resistant to or intolerant to prior therapy that included imatinib (Gleevec)</li> <li>Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL) with resistance or intolerance to prior therapy</li> </ul>	<p>CML (<i>chronic phase</i>): 100 mg PO daily</p> <p>CML (<i>accelerated or blast phase</i>): 70 mg PO BID</p> <p>Ph+ALL: 70 mg PO BID</p>	Gastrointestinal stromal tumor (GIST), multiple myeloma, chronic lymphocytic leukemia, prostate cancer
imatinib (Gleevec <sup>®</sup> ) <sup>[5]</sup>	5/2001	7/2015	<ul style="list-style-type: none"> <li>Ph+CML (all phases)</li> <li>Ph+ALL (relapsed or refractory)</li> <li>Myelodysplastic or myeloproliferative diseases w/ PDGFR gene re-arrangements</li> <li>Aggressive systemic mastocytosis (without the c-Kit mutation)</li> <li>Hypereosinophilic syndrome and/or chronic eosinophilic leukemia</li> <li>Unresectable, recurrent, and/or metastatic dermatofibrosarcoma protuberans</li> <li>Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST)</li> </ul>	<p>CML (chronic phase): 400 mg to 600 mg PO daily</p> <p>CML (<i>accelerated or blastic phase</i>): 600 mg PO daily to 400 mg PO BID</p>	Ph+ALL (newly diagnosed), meta-static melanoma, myelofibrosis, polycythemia vera, rheumatoid arthritis
nilotinib (Tasigna <sup>®</sup> ) <sup>[3]</sup>	10/2007	7/2023	Chronic phase and accelerated phase CML in patients resistant to or intolerant to prior therapy that included imatinib (Gleevec)	400 mg PO BID (empty stomach)	Blastic phase CML resistant or intolerant to imatinib (Gleevec)

<sup>a</sup> Date applies to approval date for the original brand name medication where there are now generics available. .

<sup>b</sup> Based on patents listed in Orange Book as of 01/23/08.

<sup>c</sup> As listed in © 1974 - 2008 Thomson MICROMEDEX database or as referenced.

## References

- Schiffer CA. BCR-ABL tyrosine kinase inhibitors for chronic myelogenous leukemia. N Engl J Med. 2007;357(3):258-5.
- National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Chronic Myelogenous Leukemia v.3.2008. Available at: [http://www.nccn.org/professionals/physician\\_gls/PDF/cml.pdf](http://www.nccn.org/professionals/physician_gls/PDF/cml.pdf). Accessed on 1/28/08.
- Tasigna<sup>®</sup> (nilotinib) Prescribing Information. Novartis Pharmaceuticals Corp.: East Hanover, NJ; October 2007.
- Sprycel<sup>®</sup> (dasatinib) Prescribing Information. Bristol-Myers Squibb Company: Princeton, NJ; November 2007.
- Gleevec<sup>®</sup> (imatinib) Prescribing Information. Novartis Pharmaceuticals Corp.: East Hanover, NJ; November 2007.

6. Kantarjian HM, Giles F, Gattermann N, Bhalla K, Alimena G, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. *Blood*. 2007 Nov 15;110(10):3540-6.
7. Product Dossier: Tasigna<sup>®</sup> (nilotinib), Novartis Pharmaceuticals Corporation: East Hanover, NJ. Data reviewed January 2, 2008.
8. Novartis website [page on the internet] ©2007. Press Release, October 29, 2007: Tasigna<sup>®</sup> receives US approval providing new hope to chronic myeloid leukemia patients with resistance or intolerance to existing therapies. Available at: <http://www.novartis.com/newsroom/index.shtml>. Accessed on December 31, 2007.